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Original Article

The Clinical Outcomes of Cervical Spine Chordoma: A Nationwide Multicenter Retrospective Study

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Objective: Chordoma, a rare malignant tumor originating from embryonal notochord remnants, exhibits high resistance to conventional treatments, making surgical resection imperative. However, the factors influencing prognosis specifically for cervical spine chordoma have not been clearly identified. We investigate the prognosis of cervical spine chordoma with factors influential in a nationwide multicenter retrospective study.
Methods: This study included all patients diagnosed with cervical spine chordoma at 7 tertiary referral centers from January 1998 to March 2023, excluding those with clivus and thoracic spine chordomas extending into the cervical spine. Local recurrence (LR) was identified through follow-up magnetic resonance imaging, either as reappearance in completely resected tumors or regrowth in residual tumors. The study assessed LR and overall survival, analyzing factors influencing LR and death.
Results: Forty-five patients with cervical spine chordoma had a mean age of 46.4 years. Over a median follow-up of 52 months, LR and distant metastasis were observed in 21 (46.7%) and 4 patients (8.9%), respectively, and 16 patients (36%) were confirmed dead. The 5-year and 10-year cumulative LR rates were 51.3% and 60%, respectively, while the 5-year and 10-year survival rates were 82% and 53%. Age was the only significant factor affecting mortality (hazard ratio, 1.04; 95% confidence interval, 1.04–1.07; p = 0.015). Notably, the degree of resection and adjuvant therapy did not statistically significantly impact local tumor control and mortality.
Conclusion: This study, the largest multicenter retrospective analysis of cervical spine chordoma in Korea, identified age as the only factor significantly affecting patient survival.

Keywords: Cervical spine, Chordoma, Surgery, Treatment outcome, Recurrence, Survival rate

INTRODUCTION

Chordoma is a rare malignant tumor, exhibiting an incidence rate of 0.1 cases per 100,000 individuals annually and accounting for 1% to 4% of all bone tumors.[1-3] However, it accounts for approximately 20% of all primary malignant tumors originating in bone.[4] Chordoma originates from embryonal notochord remnants and predominantly occurs within the axial skeleton.[5,6] Chordomas most frequently arise in the sacrum and skull base, with approximately 10%–30% occurring in the mobile spine (C1–L5) and about 10% in the cervical spine.[7,8] Chordoma exhibits high resistance to conventional radiotherapy and chemotherapy, making surgical resection the primary treatment modality.[9] Chordoma is characterized by slow, expansile growth and has a propensity to infiltrate local bone and adjacent soft tissue, which leads to a high likelihood of recurrence and seeding even after surgical resection.[4] Chordomas occurring in the spine are most commonly found in the sacrum, and previous literature has reported on the prognosis of sacral chordomas, as well as factors related to their prognosis.[10,11] The 5-year overall survival (OS) rate for sacral chordoma is reported to be between 70%–92%, and the 5-year progression-free survival (PFS) rate ranges from 48%–71%.[12] Previously reported prognostic factors in the literature include high sacral location, age, extent of tumor invasion, and history of previous intralesional surgery.[13-15] However, the management of cervical spine chordomas presents significant challenges due to the proximity of adjacent vital structures.[16] Additionally, the relatively rare incidence of cervical spine chordomas contributes to a scarcity of literature analyzing the prognosis and prognostic factors, resulting in a lack of consensus in the field. This study aims to evaluate the prognosis of cervical spine chordomas and investigate the contributing factors through a nationwide multicenter retrospective analysis.

MATERIALS AND METHODS

1. Study Design

From January 1998 to March 2023, all patients who underwent surgical resection or biopsy of pathologically confirmed cervical spine chordomas at 7 tertiary referral centers were included in this study. Cervical spine chordoma is defined as a tumor whose epicenter is located within the cervical spine. The 7 patients with clival chordoma extending into the cervical spine were excluded from the analysis. Similarly, one patient with thoracic spine chordoma that extended into the cervical spine was also excluded from the analysis (Supplementary Fig. 1). Patients duplicated across the datasets from various institutions were identified and subsequently excluded from the analysis. Our Institutional Review Board waived the requirement for informed consent and approved the study protocol and chart review (approval No. H-2306-175-1443). All investigations were conducted in accordance with our Institutional Review Board of guidelines and regulations.

2. Data Collection

Through a retrospective review of prospectively collected medical records, data on age at surgery or biopsy, sex, clinical presenting symptoms (categorized by pain, motor deficit, sensory deficit, local mass effect and incidental findings), duration of illness were obtained. The maximum diameter of the tumor was measured based on the greatest anterior-posterior diameter on axial images from preoperative contrast-enhanced T1-weighted and T2-weight magnetic resonance (MR) images. The radial and concentric distribution was staged using the Weinstein-Boriani-Biagnini (WBB) staging system.[17]

Complete tumor resection was categorized into *en bloc* resection and intralesional total resection based on surgical findings. Total resection was evaluated based on surgical findings and postoperative contrast-enhanced T1-weighted and T2-weighted MR images. Subtotal resection was defined as cases where more than 80% of the tumor was removed. Cases where only a needle biopsy was performed were classified as biopsy only. Patients underwent regular follow-up and MR imaging postoperatively to find out local recurrence (LR) or distant metastasis. Improvements in presenting symptoms prior to surgery were assessed and recorded. Additionally, surgical-related complications occurring after the procedure were collected. The final status of the primary disease during the follow-up period was assessed by reviewing the last treatment received by the patients and the last MR imaging conducted.

3. Surgery and Adjuvant Therapy

The surgical approach for cervical spine chordoma was determined at each institution based on the disease extent. Cases in which a tumor was partially removed via an anterior or posterior approach, followed by another surgery within 3 months without tumor regrowth, were defined as staged operations. The objective of the surgery was to achieve *en bloc* resection without tumor capsule violation. However, when *en bloc* resection was not feasible, the goal was to completely remove the tumor using a piecemeal resection. Perioperative adjuvant therapy was administered in cases with residual tumors, significant extracom-

partmental portions, or based on the surgeon's discretion. The treatment modalities employed included radiation, radiosurgery, and proton therapy. The choice of treatment modality was influenced by the equipment available at each institution and the preferences of the patients. Depending on these factors, treatments were conducted either at the institution where the surgery took place or, when necessary, patients were transferred to other institutions for further treatment. For LR, treatment involved surgery, radiation, radiosurgery, and proton therapy, either singly or in combination, based on the discretion of each institution. For distant metastasis, treatment options included surgery, radiation, radiosurgery, targeted therapy, and chemotherapy, either alone or in combination.

4. Analysis of LR and Survival

LR was defined as the detection of tumor reappearance on follow-up MR imaging for tumors that had been completely resected or the observation of regrowth in residual tumors on follow-up MR imaging. In cases of patient death or loss of follow-up, the date of the last available follow-up was used for censoring. OS was defined as the period from surgery to death, with the date of the last available follow-up used for censoring in cases of follow-up loss. The impact of age, sex, duration of illness, maximum tumor diameter, number of involved vertebral bodies, radial distribution, concentric distribution, surgery and perioperative therapy, and total resection (*en bloc* and intralesional total resection) on LR and death were analyzed.

5. Statistical Analysis

Descriptive statistical analyses were conducted; continuous variables were examined using the mean, standard deviation, and range, or the median and interquartile range. The comparison of categorical variables was conducted using the chi-square test or Fisher exact test, while the comparison of continuous variables was performed using the independent t-test. The Fine-Gray subdistribution hazard model was employed to analyze factors affecting LR, while Cox proportional hazard model was used for factors influencing death. The proportional hazard assumption was investigated using cumulative sums of martingale residuals for Cox proportional hazard model and Schoenfeld residuals plots for the Fine-Gray model. In the multivariate analysis, variables with a p-value of <0.2 in the univariate analysis were included. Subdistribution hazard ratio (HR) of Fine-Gray subdistribution hazard model and HR for Cox proportional hazard model with a 95% confidence interval (CI) not containing 1.0, and a p-value of <0.05 were considered statistically significant. Kaplan-Meier survival analysis was utilized to assess OS, and the cumulative incidence of LR was estimated considering death as the competing event. Analyses of LR and OS excluded 3 patients who underwent biopsy only, focusing on 42 patients who received surgery; OS analysis was performed on 41 patients, excluding one who was lost to follow-up immediately after surgery. For comparing the survival curve, the log-rank test was used. All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, North Carolina, USA) and IBM SPSS Statistics ver. 29.0 (IBM Co., Armonk, NY, USA).

RESULTS

1. Demographics and Preoperative Variables

A total of 45 patients were diagnosed with cervical spine chordoma, with a mean age of 46.4 years; 30 of these patients (66.7%) were male. The most common preoperative symptom was pain, reported in 31 patients (70.5%), and followed by motor deficit in 11 patients (25%). The mean duration of illness before diagnosis was 3.9 months. The mean maximum diameter of the tumors was 3.9 cm, with the median radial distribution according to WBB staging being 6, and the median concentric distribution being 4. Involvement of the vertebral artery canal was observed in 28 patients (68.3%) (Table 1). The distribution of ver-

Table 1. Baseline characteristics (N = 45)

Variable	Value
Age (yr)	46.4 ± 22.0 (7–86)
Male sex	30 (66.7)
Clinical presenting symptom	
Pain	31/44 (70.5)
Motor deficit	11/44 (25)
Sensory deficit	8/44 (18.2)
Local mass effects	6/44 (13.6)
Incidental	2/44 (4.5)
Duration of illness (mo) (n = 39)	3.9 (2.0–8.0)
Radiological parameters	
Maximal tumor diameter (cm) (n = 41)	3.9 ± 1.7 (1.0–9.4)
Number of involved vertebral bodies	2 (2–3)
Radial distribution by WBB staging (n = 41)	6 (4–9)
Concentric distribution by WBB staging (n = 41)	4 (3–4)
Vertebral artery canal involvement (n = 41)	28 (68.3)

Values are presented as mean ± standard deviation (range), number (%), or median (interquartile range).
WBB, Weinstein-Boriani-Biagnini.

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tebral bodies involved in cervical spine chordomas is presented in Fig. 1A. The total number of vertebral body involvements amounted to 106, with C2 involvement being the most prevalent at 32.1% (34 out of 106), followed by C3 involvement at 25.5% (27 out of 106). The distribution of the epicenter for cervical spine chordomas is presented in Fig. 1B. The most common epicenter was C2 at 66.7% (30 out of 45), followed by C3 at 11.1% (5 out of 45).

2. Details of Treatment Protocol

Three patients (6.7%) underwent biopsy only, while 42 patients (93.3%) received surgical resection. Among these, 2 patients (5% of 40 patients) underwent preoperative vertebral artery embolization, and 1 patient (2.2%) received neoadjuvant radiation. The initial surgery was an anterior approach for 10 patients (23.8% of 42 patients), and a posterior approach and staged surgery for 16 patients each (38.1% of 42 patients). Thirty patients (71.4% of 42 patients) underwent adjuvant therapy postoperatively, with radiation being the most common in 17 patients (56.7% of 30 patients), followed by proton therapy for 11 patients (36.7% of 30 patients). LR was managed with surgery, surgery plus adjuvant therapy, radiation therapy, and radiosurgery, while distant metastasis was treated with surgery, radiation therapy, radiosurgery, proton therapy, chemotherapy, and targeted therapy (Table 2). The treatment flow of the patients the status of the tumor and survival period at the last follow-up are depicted in Fig. 2.

3. Oncologic Outcomes

Complete tumor resection was achieved in 14 patients (35% of 40 patients), with 2 (14.3% of 14 patients) undergoing *en bloc* resection and 12 (85.7% of 14 patients) receiving intralesional total resection. Postoperative, pain improved in 22 patients (73.3% of 30 patients), and motor deficit improved in 8 (80% of 10 patients). One patient (2.4% of 42 patients) died from gastrointestinal bleeding postoperatively. Other complications included

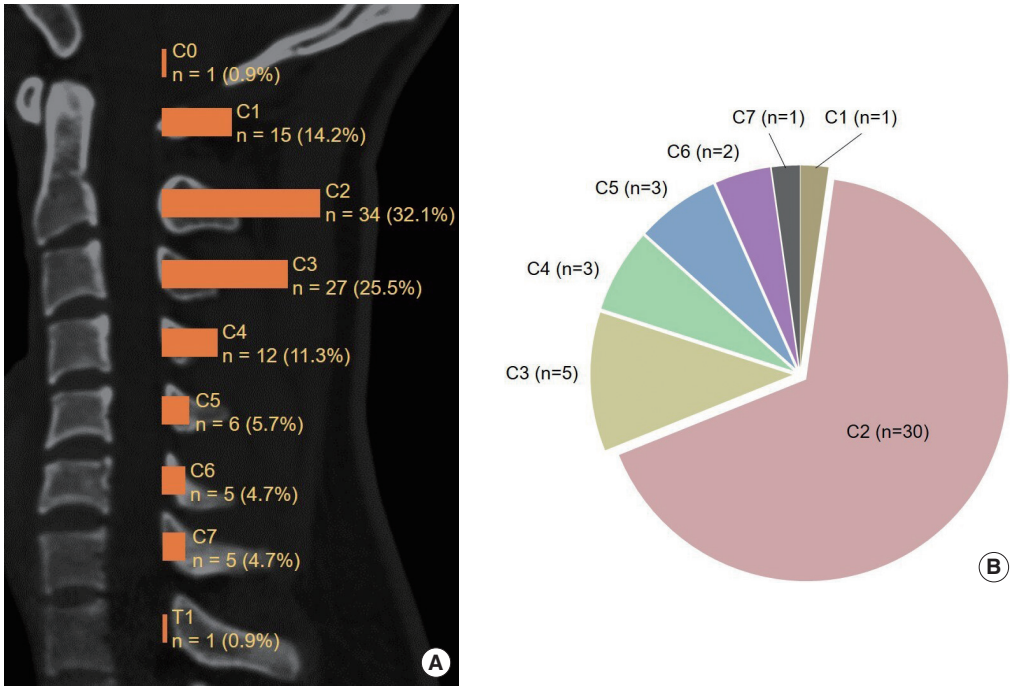

Fig. 1. The distribution of cervical spine chordomas. (A) The distribution of vertebral body involvement in cervical spine chordoma is as follows (per total number of vertebral involvement, 106): C2 involvement was the most common, observed in 34 patients (32.1%, 34 out of 106), followed by C3 involvement in 27 patients (25.5%, 27 out of 106). C1 involvement was noted in 15 patients (14.2%), while C4 involvement was seen in 12 patients (11.3%). Involvement of C5 was observed in 6 patients (5.7%). Both C6 and C7 showed involvement in 5 patients each (4.7%). Additionally, C0 and T1 involvement were each observed in 1 patient (0.9%). C0 and T1 level chordomas were cases where cervical spine chordoma extended to the C0 and T1 levels, respectively. (B) The distribution of epicenter for cervical spine chordomas is as follows (per total number of patients, 45): C2 was the most common, observed in 30 patients (66.7%), followed by C3 in 5 patients (11.1%). C4 and C5 were involved in 3 patients (6.7%) each, while C6 was involved in 2 patients (4.4%). C1 and C7 were the epicenter in 1 patient (2.2%) each.

Table 2. Details of treatment protocol in cervical spine chordoma (N = 45)

Variable	Value
Biopsy only	3 (6.7)
Preoperative vertebral artery embolization	2/40 (5.0)
Neoadjuvant radiation	1 (2.2)
Surgical approach	
Anterior	10/42 (23.8)
Posterior	16/42 (38.1)
Staged	16/42 (38.1)
Adjuvant therapy	
Radiation	17/30 (56.7)
Proton	11/30 (36.7)
Combined radiation and proton	1/30 (3.3)
Radiosurgery	1/30 (3.3)
Treatment after 1st local recurrence	
Surgery	6/21 (28.6)
Surgery and adjuvant therapy	9/21 (42.9)
Radiation	2/21 (9.5)
Follow-up loss	4/21 (19.0)
Treatment after 2nd local recurrence	
Surgery	3/9 (33.3)
Surgery and adjuvant therapy	1/9 (11.1)
Radiation or radiosurgery	4/9 (44.4)
Follow-up loss	1/9 (11.1)
Treatment after 3rd local recurrence	
Surgery	2/3 (66.7)
Radiosurgery	1/3 (33.3)
Treatment for distant metastasis	
Surgery	1/4 (25.0)
Radiation and radiosurgery	1/4 (25.0)
Targeted therapy	1/4 (25.0)
Radiation and proton, chemotherapy	1/4 (25.0)

Values are presented as number (%).

one case each of instrument failure requiring revision surgery, cerebrospinal fluid leakage, pontine infarction, meningitis, and vocal cord palsy. The median follow-up period was 52 months, with LR observed in 21 patients (46.7%) and distant metastasis in 4 (8.9%). The median time to distant metastasis from the first surgery was 27 months. Sixteen patients (35.6%) died. When comparing methods of total resection, no significant differences were found in LR, death, and OS between *en bloc* resection and intralesional total resection. Similarly, when comparing modalities of adjuvant therapy, there were no significant differences in LR, death, and OS between adjuvant radiation and proton therapy (Supplementary Table 1 and Supplementary Fig. 2). There were no significant differences in the radiation doses of adjuvant therapy in terms of LR and death (Supplementary Table 2). Those with LR or distant metastasis, excluding those lost to follow-up, received appropriate treatment, resulting in stable disease for 36 patients (80%) and progressive disease for 9 (20%) at the last follow-up (Table 3). Additionally, while direct comparisons are limited, the outcomes of patients with clivus to cervical spine chordoma and cervicothoracic spine chordoma, who were excluded from this study, are presented in Supplementary Table 3 and Supplementary Fig. 3.

4. Prognostic Factors for LR and Survival

Factors influencing LR included age, gender, duration of illness, maximum tumor diameter, tumor extent, surgery and perioperative adjuvant therapy, and total resection, none of which were significant (Table 4). In multivariate Cox proportioinal hazard model, age was the only factor affecting death (HR, 1.04; 95% CI, 1.01–1.07; p = 0.015) (Table 5). The 5-year cumulative LR rate was 51.3% (95% CI, 32.8%–67.1%), and the 10-year cumulative LR rate was 60% (95% CI, 34.7%–78.2%). The 5-year OS rate was 82% (95% CI, 64.1%–91.8%), and the 10-year OS rate was 53% (95% CI, 30.5%–71.3%). When comparing OS based on the mean age of 46.4 years, the 2 groups demonstrated a significant difference (p = 0.005), with the patient group under 20 years old exhibiting better OS than the patient group over 60 years old (p = 0.039) (Fig. 3).

DISCUSSION

This study represents the first multicenter retrospective analysis in the Korea on the treatment and prognosis of cervical spine chordoma. Despite the low incidence of cervical spine chordoma, this study conducted a comprehensive analysis of a total of 45 patients over an extended period. Of these, 42 patients (93.3%) underwent surgery, with complete tumor resection achieved in 14 cases (35% of 40 patients). Postoperatively, 30 patients (71.4%) received adjuvant therapy. Regular follow-up was conducted, with LR observed in 21 patients (46.7%). The 5-year cumulative recurrence rate was 51.3%, and the 10-year rate was 60%. Treatments for LR included surgery and radiation therapy among other appropriate modalities, while distant metastasis occurred in 4 patients (8.9%), with a median time of 27 months from the first surgery to metastasis occurrence. Distant metastasis was treated with surgery, radiation therapy, che-

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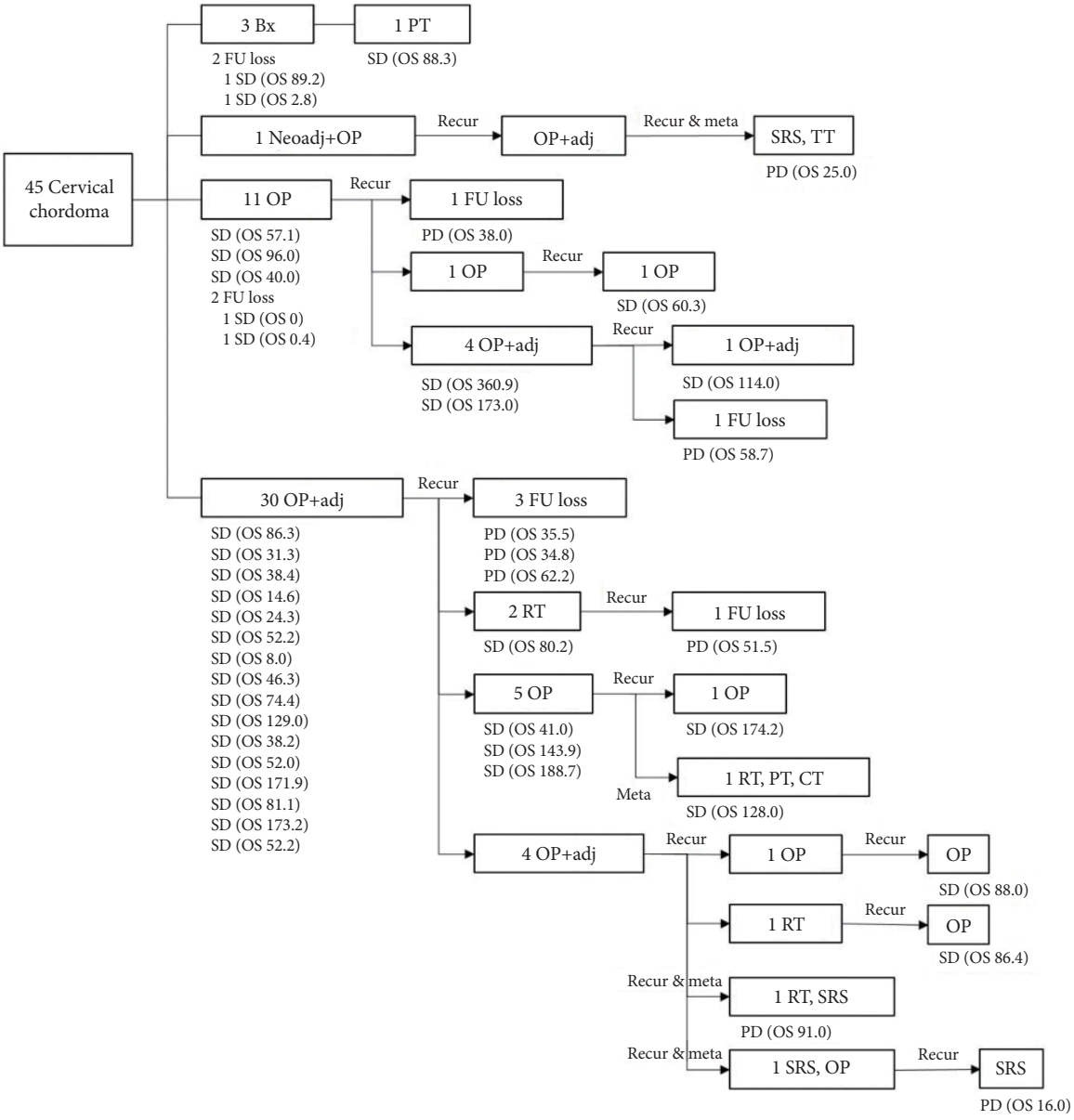

Fig. 2. Schematic overview of the treatment and outcomes for 45 cervical spine chordomas. Among a total of 45 patients, 3 underwent biopsy, 2 of whom were lost to follow-up (FU), and the remaining one received proton therapy (PT). The other 42 patients underwent operation (OP). One patient received neoadjuvant therapy (Neoadj) and OP, but experienced a recurrence, leading to a secondary OP and adjuvant therapy (adj). Following another recurrence and the detection of distant metastasis, the patient underwent stereotactic radiosurgery (SRS) and targeted therapy (TT). Of the 11 patients who underwent OP alone, 2 were lost to FU, and recurrence occurred in 6 patients. One of the patients who experienced a recurrence was subsequently lost to FU. One patient experienced a recurrence after secondary OP and subsequently underwent tertiary OP. Four patients received secondary OP and adj; of these, 2 experienced further recurrences, 1 was lost to FU, and another underwent tertiary OP and adj. Thirty patients received OP and adj, with 14 experiencing recurrences; 3 of these were lost to FU. Two patients received radiation therapy (RT), 1 of whom experienced a recurrence and was subsequently lost to FU. Five patients underwent secondary OP; of these, one had a recurrence and received tertiary OP, while another, diagnosed with distant metastasis, underwent RT, PT, and chemotherapy (CT). Four patients underwent secondary OP and adj, all of whom experienced recurrences. One patient underwent tertiary OP following a recurrence and subsequently required quaternary OP. Another patient received RT and, after a recurrence, underwent tertiary OP. Recurrences and distant metastasis were confirmed in 2 patients: one received RT and SRS, and the other underwent tertiary OP and SRS, followed by recurrence and additional SRS. Bx, biopsy; SD, stable disease; OS, overall survival; PD, progressive disease.

Table 3. Oncologic outcomes of cervical spine chordoma (N = 45)

Variable	Value
Degree of resection	
En bloc resection	2/40 (5)
Intralesional total resection	12/40 (30)
STR	14/40 (35)
PR	12/40 (30)
Improvement of preoperative symptoms	
Pain	22/30 (73.3)
Motor deficit	8/10 (80.0)
Sensory deficit	5/7 (71.4)
Local mass effects	3/3 (100)
Complication	
Death	1/42 (2.4)
Instrument failure	1/42 (2.4)
CSF leakage	1/42 (2.4)
Pontine infarction	1/42 (2.4)
Meningitis	1/42 (2.4)
Vocal cord palsy	1/42 (2.4)
Follow-up duration (mo)	52.0 (31.6–88.2)
Local recurrence	21 (46.7)
Distant metastasis	4 (8.9)
The period from initial surgery to distant metastasis (mo)	27 (12.5–34.7)
Death	16 (35.6)
Last follow-up status	
SD	36 (80.0)
PD	9 (20.0)

Values are presented as number (%) or median (interquartile range).
STR, subtotal resection; PR, partial resection; CSF, cerebrospinal fluid; SD, stable disease; PD, progressive disease.

motherapy, and targeted therapy. The 5-year survival rate for cervical chordoma was 82%, and the 10-year survival rate was 53%. Analysis of prognostic factors found no statistically significant factors affecting LR, with the only statistically significant factor influencing death being the age at the time of surgery.

The 5-year survival rate for mobile spine chordoma is reported to be between 54%–71%, and the 10-year survival rate ranges from 21%–58%.[8,18] The most critical factor affecting the prognosis of mobile spine chordoma is the control of the primary tumor.[6] Akinduro et al.[16] reported in a meta-analysis of cervical spine chordoma that total resection of the tumor has a positive impact on local control and OS. In the case of cervical spine chordomas, the adjacent vital structure of the tumor makes complete surgical resection challenging.[19] Complete tumor resec-

Table 4. Fine-Gray subdistribution hazard model for local recurrence

Variable	Univariate		p-value
	sHR	95% CI	
Age	1.00	0.98–1.02	0.838
Male sex	0.87	0.35–2.18	0.765
Duration of illness	0.98	0.93–1.03	0.349
Maximal tumor diameter	1.04	0.80–1.34	0.796
No. of involved vertebral bodies	1.08	0.68–1.73	0.744
Radial distribution by WBB staging	1.03	0.90–1.19	0.636
Concentric distribution by WBB staging	0.93	0.50–1.75	0.824
Surgery and perioperative adjuvant therapy	0.58	0.22–1.54	0.276
Total resection	0.80	0.32–2.00	0.634

sHR, subdistribution hazard ratio; CI, confidence interval; WBB, Weinstein-Boriani-Biagnini.

Table 5. Cox proportional hazard model for death

Variable	Univariate		p-value	Multivariate		p-value
	HR	95% CI		HR	95% CI	
Age	1.05	1.01–1.08	0.008	1.04	1.01–1.07	0.015
Male	0.91	0.31–2.68	0.869	-	-	-
Duration of illness	1.00	0.95–1.05	0.861	-	-	-
Maximal tumor diameter	1.27	0.94–1.72	0.118	1.44	0.97–2.14	0.073
Number of involved vertebral bodies	0.78	0.38–1.64	0.514	-	-	-
Radial distribution by WBB staging	0.91	0.75–1.11	0.346	-	-	-
Concentric distribution by WBB staging	1.26	0.66–2.41	0.484	-	-	-
Surgery and perioperative adjuvant therapy	0.87	0.28–2.73	0.808	-	-	-
Total resection	0.49	0.14–1.73	0.268	-	-	-

HR, hazard ratio; CI, confidence interval; WBB, Weinstein-Boriani-Biagnini.

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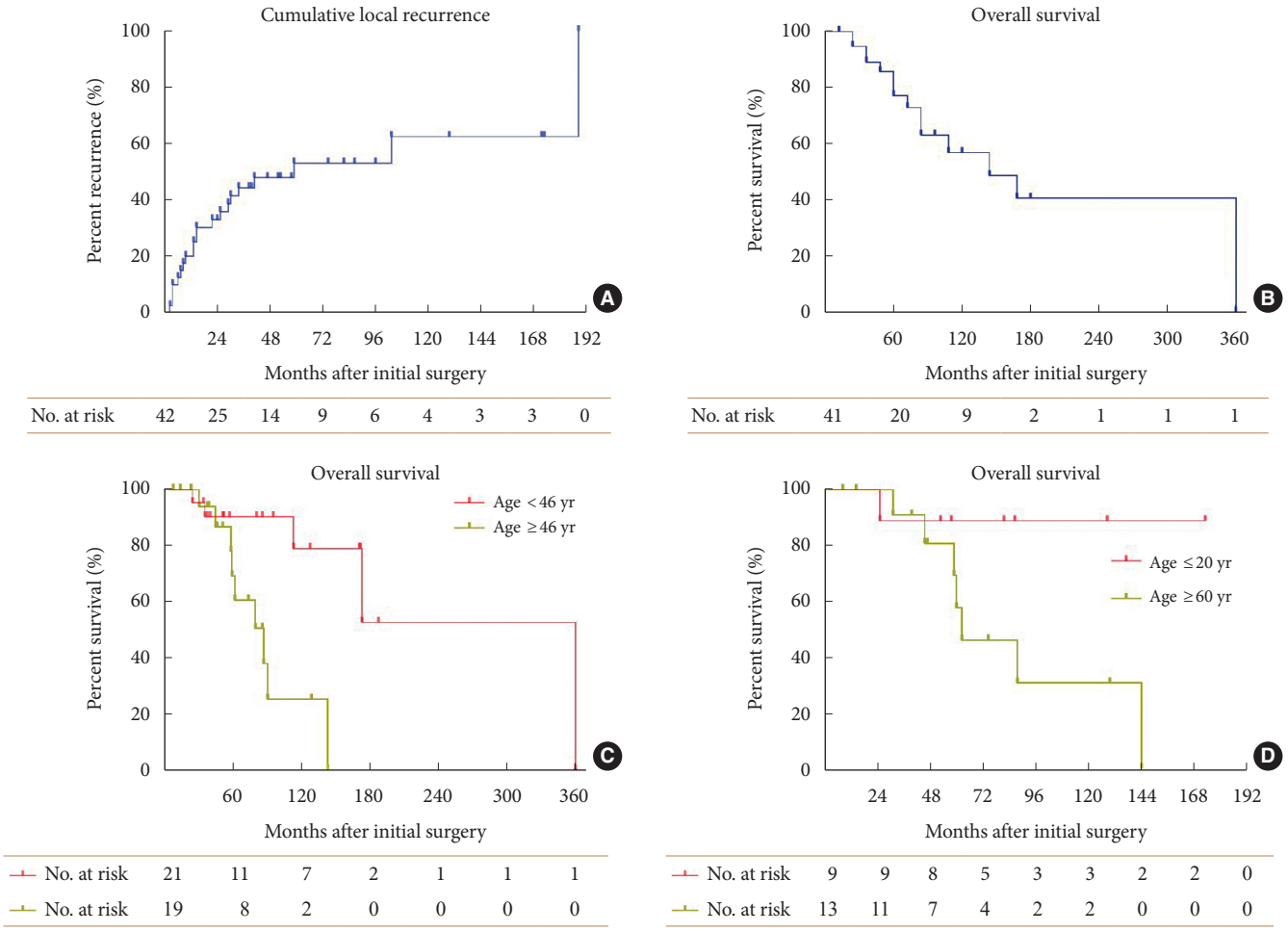

Fig. 3. Cumulative incidence of local recurrence (LR) and overall survival of cervical spine chordomas. (A) The cumulative incidence of LR among 42 patients with cervical spine chordoma was reported as follows: the 5-year cumulative LR rate was 51.3% (95% confidence interval [CI], 32.8%–67.1%), and the 10-year cumulative LR rate was 60% (95% CI, 34.7%–78.2%). (B) The overall survival (OS) after initial surgery for 41 patients with cervical spine chordoma was as follows: the 5-year OS rate was 82% (95% CI, 64.1%–91.8%), and the 10-year OS rate was 53% (95% CI, 30.5%–71.3%). (C) Comparing OS after initial surgery between patients aged 46 years and older and those under 46 years old ($p < 0.005$). The median survival for patients under 46 years was 81.6 months, while the median survival for those aged 46 years and older was 51.6 months. (D) Comparing OS after initial surgery in patients 20 years of age or younger and those 60 years of age or older ($p = 0.039$). The median survival for patients 20 years or younger was 81.6 months, while the median survival for those 60 years or older was 46.8 months.

tion can be achieved through 2 methods: *en bloc* spondylectomy and intralesional total resection. However, the difference in prognosis between these 2 methods for cervical spine chordoma is not clear, and *en bloc* spondylectomy may lead to a higher rate of morbidity and mortality.[16,20,21] Therefore, considering not only the oncologic outcome but also the patient's functional status, intralesional total resection may be more appropriate for cervical spine chordoma.[4,21,22] In this study, total resection (including both *en bloc* and intralesional total resection) did not significantly impact LR or death. The determination of total resection was made by considering both surgical findings and postoperative MR imaging. However, the complex anatomy of the neck might have posed challenges in detecting residual tumors on MR imaging. It is possible that small remnants of the tumor were not visible on MR imaging, leading to an underestimation of the actual extent of tumor persistence. Achieving *en bloc* resection in cervical spine chordoma is almost tantamount to an impossibility, and fundamentally, accomplishing intralesional total resection also presents considerable challenges. It is impossible to sacrifice the spinal cord for tumor resection, and sacrificing the cervical roots can lead to postoperative weakness or respiratory difficulty.[23] Occlusion of the bilateral vertebral

arteries can lead to fatal brainstem infarctions, and even injury to a unilateral vertebral artery can result in symptomatic complications.[24,25] These factors are likely to have influenced the local control of cervical spine chordoma. In the meta-analysis of cervical spine chordoma presented, an analysis of 161 patients from a total of 13 studies was conducted, among which total resection was achieved in 118 patients (73.3%).[16] However, in this study, total resection was achieved in 14 individuals (35% of 40 patients), and when considering the institution of the author who conducted the meta-analysis alone, total resection was accomplished in 7 patients (31.8% of 22 patients).[16] Given this data, the total resection rate of 73.3% reported in the meta-analysis may have been overstated compared to actual figures, and the impact of total resection on the prognosis of cervical spine chordoma may have been exaggerated in the analysis. Therefore, the relationship between total resection and the prognosis of cervical spine chordoma, as demonstrated in this study, may well reflect the current standard, providing ample reason to reconsider the conclusions drawn from previous analyses.

Skull base chordomas, similar to cervical spine chordomas, frequently encounter limitations in complete resection due to the adjacent vital structure of the tumor. The 3-year PFS for skull base chordomas is reported to be 61%, the 5-year PFS is 51%, the 3-year OS is 89.7%, and the 5-year OS is 47.6%.[26] In the treatment of clivus chordomas, complete resection of the tumor is a significant factor in prognosis. However, when considering functional outcomes, the current standard of care is deemed to be maximal safe resection followed by adjuvant therapy.[27] Adjuvant therapy for residual tumors in skull base chordoma can enhance PFS. Furthermore, adjuvant therapy performed after total resection also aids in preventing LR.[28-31] Previous literature comparing outcomes between patients with cervical spine chordoma who underwent surgical resection alone and those who received surgical resection followed by adjuvant therapy is limited. Zhou et al.[32] reported that adjuvant therapy enhances PFS in case with positive margin in an integrative analysis of 682 patients with spine chordoma. However, they also noted that adjuvant therapy could decrease PFS in cases with negative margins. Meng et al.[33] analyzed the prognosis of patients with spinal chordoma and reported that adjuvant therapy did not have a significant impact on the control of LR. In this study, adjuvant therapy demonstrated no significant impact on the prognosis of cervical spine chordoma. Furthermore, when patients who underwent total resection were subgrouped, there was no difference in LR and death based on the presence or absence of adjuvant therapy. In the case of cervical spine chordoma, the presence of critical organs at risk, such as the spinal cord and brainstem, may limit the feasibility of administering sufficient radiation doses.[34] However, advancements in radiation technology have enabled more effective and safer delivery of radiation to tumors. Recent studies have suggested that radiation doses exceeding 65 Gy can improve the survival of chordoma patients.[35] Therefore, this study suggests that there may be differences in adjuvant therapy strategies between patients in the past and more recent patients, as well as variations in adjuvant therapy strategies among different institutions. Additionally, the complex anatomical or adjacent vital structures can pose challenges in achieving accurate radiation target volume and dose homogeneity.[36,37] Surgical resection can cause distortions in the normal anatomical structures, and differentiating between postoperative changes and residual tumor for targeted radiation may be limited.[38] These factors are likely to have influenced the local control of cervical spine chordoma.

The impact of age on the prognosis of chordoma is variably reported across the literature. Yoneoka et al.[39] analyzed the outcomes of 13 patients with skull base chordoma, reporting that younger patients, those under the age of 20, exhibited a more favorable clinical course. Noël et al.[40] analyzed the prognosis of 67 patients with skull base and cervical spine chordoma or chondrosarcoma, reporting that younger age, specifically below 40–50 years, was a factor that positively influenced local control. In this study, the mean age of the patients was 46.4 years, which, considering that the peak incidence age for chordoma is 60 years, indicates that the patients included in this study were relatively young. Age was the sole factor influencing mortality, with older age having a negative impact on survival outcomes. In patients under the age of 46.4 years, total resection was achieved in 50% (10 of 20 patients), whereas in patients aged 46.4 years and above, total resection was achieved in 20% (4 of 20 patients) ($p = 0.047$). The relative lack of comorbidities in younger patients, coupled with the ability to attempt more aggressive tumor removal in younger patients, may have influenced the outcomes. Conversely, there are reports indicating that the clinical outcomes of chordoma in younger patients are not as favorable when compared to those in older age groups. Yasuda et al.[41] analyzed the prognosis of 40 patients with skull base chordoma and cervical spine chordoma, reporting that patients under the age of 42 demonstrated lower 5-year OS rates. Notably, those under the age of 25 experienced rapid tumor relapse and death. Additionally, although rare in children, chordomas in this age group often exhibit atypical pathology and are clinically characterized by rapid tumor progression and more

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aggressive features, leading to a reported poor prognosis.[42,43]

This study is a multicenter retrospective analysis of cervical spine chordoma. Due to the low incidence of cervical spine chordoma, patients were recruited over a long period, and the retrospective analysis led to missing or unverifiable data, including records and imaging data from many years ago. Secondly, due to the lack of comprehensive molecular genetic analysis, it was not possible to analyze the impact of the genetic and molecular characteristics on the prognosis of cervical spine chordoma. Thirdly, over time, advancements in surgical techniques and technological improvements in adjuvant therapy may have led to differences in treatment strategies between past and recent patients. Fourthly, the neurological complications that could arise from adjuvant therapy were not analyzed in the study. Lastly, it was not possible to compare specific indicators of adjuvant therapy, such as target volume and effective radiation dose. These limitations likely contributed to the inability to identify significant factors related to LR and death, other than age. Therefore, it is anticipated that prospective, systematic data collection could reveal significant factors associated with LR and death.

CONCLUSION

This nationwide multicenter retrospective study presented the clinical outcomes for cervical spine chordoma, revealing a 5-year cumulative LR rate was 51.3%, a 10-year cumulative LR rate was 60%, a 5-year OS rate of 82%, and a 10-year survival rate of 53%. The degree of resection and adjuvant therapy did not statistically significantly impact local tumor control and mortality. Age was the only factor found to statistically significantly affect survival. Although there are several limitations hindering the conclusiveness of these findings, this study is significant in that it is the largest case series analysis of cervical spinal chordomas depicting the clinical outcomes currently achieved in the Korea.

NOTES

Supplementary Materials: Supplementary Tables 1-3 and Figs. 1-3 can be found via https://doi.org/10.14245/ns.2448448.224.

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Supplementary Table 1. Comparison of local recurrence and death based on the methods of total resection and the modalities of adjuvant therapy

	En bloc resection (n = 2)	Intralesional total resection (n = 12)	p-value	Adjuvant radiation therapy (n = 18)†	Adjuvant proton therapy (n = 11)	p-value
Local recurrence	0 (0)	6 (50.0)	0.473	9 (50.0)	5 (45.5)	0.812
Death	0 (0)	3 (25.0)	1.000	5 (27.8)	4 (36.4)	0.694

Values are presented as number (%).
†One patient who received both adjuvant radiation and proton therapy was excluded from the analysis.

Supplementary Table 2. Comparison of radiation doses in adjuvant therapy for local recurrence and death

	Local recurrence (n = 10)	No local recurrence (n = 11)	p-value	Death (n = 7)	Survival (n = 14)	p-value
Radiation dose	61.0 ± 10.2 (40–72)	61.3 ± 11.1 (34.5–70.4)	0.951	63.6 ± 10.9 (40–72)	60.0 ± 10.4 (34.5–70.4)	0.464

Values are presented as mean ± standard deviation (range).

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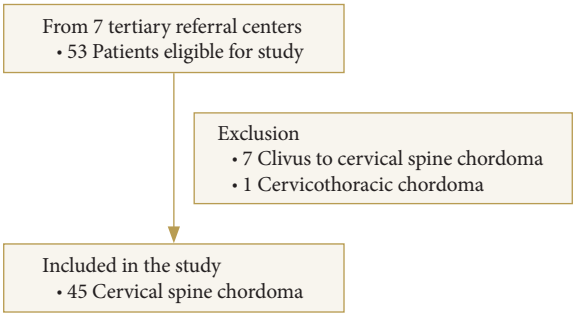
Supplementary Table 3. The patients of clivus to cervical spine and cervicothoracic spine chordoma

No.	Age (yr)	Sex	Tumor extent	Extent of resection of initial surgery	Adjuvant therapy	FU duration (mo)	Local recurrence	Death
1	19	M	Clivus to cervical spine	GTR	Radiation	44.8	No recurrence	Survival
2	40	M	Clivus to cervical spine	GTR	Radiation	87.8	Recurrence	Survival
3	28	M	Clivus to cervical spine	STR	NA	92.4	Recurrence	Survival
4	51	F	Clivus to cervical spine	GTR	Radiation	61.1	Recurrence	Death
5*	30	F	Clivus to cervical spine	NA	NA	109.9	Recurrence	Survival
6	23	M	Clivus to cervical spine	STR	Radiation	43.2	Recurrence	Death
7	37	M	Clivus to cervical spine	GTR	Proton	33.1	Recurrence	Death
8	52	F	Cervicothracic spine	GTR	Radiation	159.0	Recurrence	Survival

FU, follow-up; GTR, gross total resection; STR, subtotal resection; NA, not applicable.
*The patient underwent proton therapy without pathologic confirmation and subsequently underwent surgery due to regrowth.



Supplementary Fig. 1. The patient inclusion flow chart. In total, 53 patients were retrospectively collected from 7 tertiary referral centers. Of these, 7 patients with clivus chordoma extending to the cervical spine and 1 patient with thoracic chordoma extending to the cervical spine were excluded. Consequently, 45 patients with cervical spine chordoma were ultimately included in this study.

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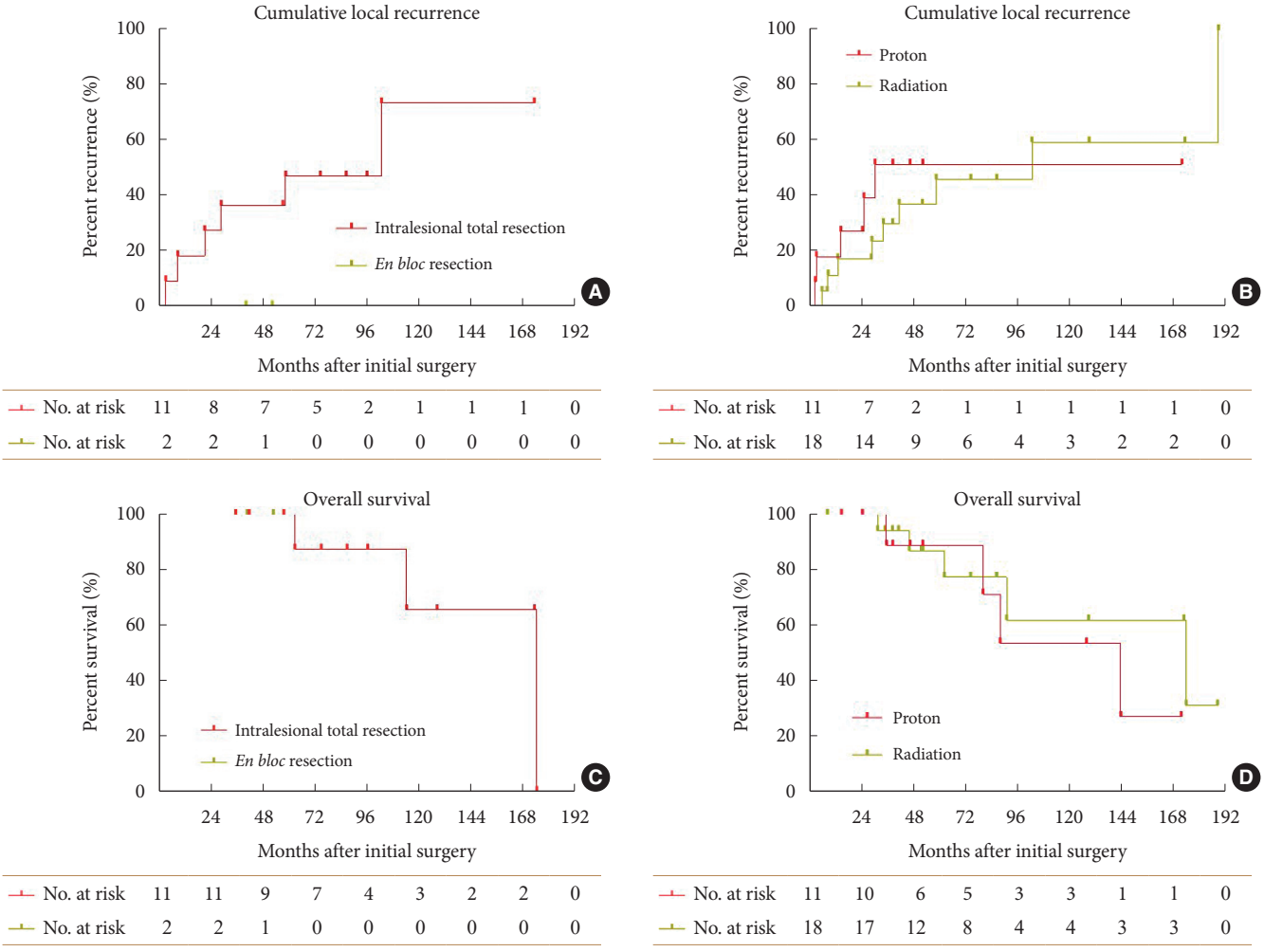
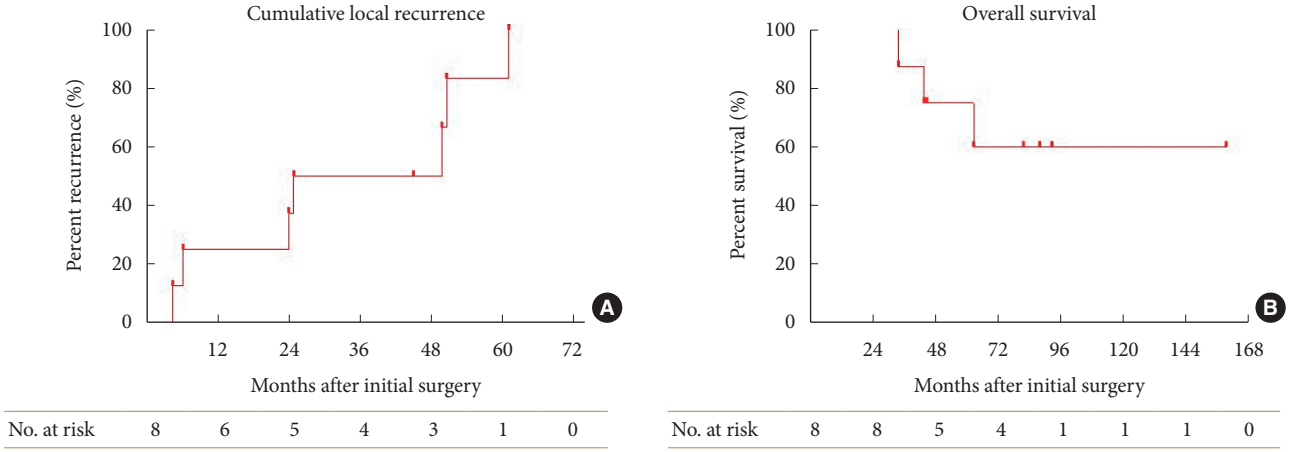


Supplementary Fig. 2. Cumulative local recurrence and overall survival of cervical spine chordomas by the methods of total resection and modalities of adjuvant therapy. (A) Comparing cumulative local recurrence (LR) after initial surgery between *en bloc* resection and intralesional total resection (p = 0.356). (B) Comparing cumulative LR after initial surgery between adjuvant radiation and proton therapy (p = 0.488). (C) Comparing overall survival (OS) after initial surgery between *en bloc* resection and intralesional total resection (p = 1.000). (D) Comparing OS after initial surgery between adjuvant radiation and proton therapy (p = 0.495).



Supplementary Fig. 3. Cumulative local recurrence and overall survival of clivus to cervical spine chordoma and cervicothoracic chordoma. (A) The 5-year cumulative local recurrence (LR) rate was 83.3% (95% CI, 4.7%–97.1%). (B) The 5-year overall survival (OS) rate was 75% (95% CI, 50.3%–100%), and the 10-year OS rate was 60% (95% CI, 33.1%–100%).

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